Claim 27 has been rejected under 35 U.S.C.§102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103 as obvious over Waldmann (Blood, 1993), as evidenced by Waldmann et al (Blood, 1995) and/or Vriessendorp. Applicants respectfully disagree with this rejection.

The Examiner asserts that the Waldmann reference (1993) inherently discloses and/or makes obvious the claimed invention. The Examiner points to Waldmann (1995) and Vriessendorp as providing evidence supporting his conclusion. Applicants respectfully disagree with this position.

As an initial matter, the use of Waldmann (1995) as "evidence" is a glaring example of hindsight. Waldmann (1995) is NOT prior art and the Examiner admits as much. The Examiner takes the position that Waldmann (1995) "is provided simply to show an inherent property of the prior art methods." Here lies the flaw in the Examiner's rationale. Waldmann (1995) does not show inherence of the prior art, but rather shows a separate experiment with new results. The Examiner is trying to import the teaching of the 1995 article into the Waldmann (1993) reference. Each reference must be viewed for what it teaches. One cannot read the Waldmann (1995) reference into the Waldmann (1993) publication. The Waldmann (1993) reference does not teach or suggest the parameters of the experiments carried out in the Waldmann (1995) publication. One skilled in the art COULD NOT deduce or "know" how to determine the dosage of ^{90}Y-conjugated anti-Tac for a patient. Further, the skilled artisan COULD NOT deduce or "know" that there is a correlation between the amount of anti-Tac and the patients' soluble IL-2R levels.

The claimed invention requires the identification and connection of three separate parameters: (1) an amount of anti-Tac, (2) an amount of ^{90}Y isotope conjugated to the anti-Tac

and (3) a correlation to soluble IL-2R levels in a patient. In order to anticipate or obviate the claimed invention, the prior art must teach or suggest at least one amount of anti-Tac within the claimed range, conjugated to at least one amount of ^{90}Y isotope within the claimed range, given to a patient having at least one amount of the soluble IL-2R within the claimed range. The Examiner has not shown this minimum level of teaching in the prior art. Therefore, the Examiner has resorted to asserting that the missing teachings were "inherent" in the cited art and uses the later-published studies to "evidence" his position. This assertion is flawed as it relates to anticipation and as it relates to obviousness.

As pointed out previously, inherency requires the missing matter be "recognized by persons of ordinary skill". *See Continental Can Co. USA, Inc. v. Monsanto Co.* (948 F.2d 1264, 1268 (Fed. Cir. 1991). In stark contrast, the claimed method is not only NOT taught or suggested by Waldmann 1993, but one skilled in the art would not have known how to determine the dosages of yttrium-90 conjugated anti-Tac based upon this reference, or any prior art reference cited by the Examiner. Waldmann (1993) describes the use of unlabeled anti-Tac at a dose of 20-50 mg, preferably 50 mg and mentions a separate study using a labeled anti-Tac at 5-15 mCi without stating any other parameters. Waldmann (1993) also describes administering the same dose of unlabeled anti-Tac to patients having varying soluble IL-2R levels. How could one skilled in the art reading this reference inherently know or even guess that there is a correlation between soluble IL-2R levels in the patient and the amount of ^{90}Y-conjugated anti-Tac? How could the skilled artisan inherently know or even guess that 5-15 mCi of ^{90}Y should be provided with 2-20 mg of anti-Tac?

Waldmann (1993) describes the use of 20-50 mg, preferably 50 mg unlabeled anti-Tac. The Examiner points out that Waldmann also states that 2-17 mg anti-Tac is "required

to yield circulating bioavailable anti-Tac". This is true. However, please notice that Waldmann(1993) is not saying that 2-17 mg are a useful *therapeutic* dosage, but rather that 2-17 mg are needed to "yield circulating bioavailable anti-Tac". Indeed for *therapeutic* purposes, Waldmann (1993) starts the clinical study using 20-50 mg, then *increases* the doses to 50 mg, stating: "In light of these early observations, to achieve a rapid saturation of IL-2R, the basic dosing schedule was altered for the final 10 patients in the group so that 50 mg anti-Tac per patient was administered on two occasions during the first week of therapy and on two occasions during the second week of therapy." [Waldmann (1993) at 1705]. In fact, Waldmann goes on to emphasize the need for this higher dose by stating: "Additional doses of 50 mg anti-Tac to maintain receptor saturation were administered to patients who made an initial partial or complete response to therapy." [*Id.*]. Finally, applicants point out that the sIL-2R levels of the patients ranged from 920-230,370 U/ml and no correlation was made between amount of unlabeled anti-Tac and sIL-2R levels. How could one skilled in the art read this and recognize, expressly or inherently, that the dosage comprises 5-15 mCi ^{90}Y-conjugated anti-Tac in a total amount of 2-20 mg anti-Tac, wherein the the dose is 2 mg total anti-Tac if said patient has sIL-2R levels of less than 2,000 units/ml, the dose is 5 mg total anti-Tac if said patient has sIL-2R levels of 2,000 - 10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has sIL-2R levels of 10,000 - 50,000 units/ml, and the dose is 20 mg of total anti-Tac if said patient has sIL-2R levels of greater than 50,000 units/ml? Clearly, the skilled artisan could not. Applicants respectfully request reconsideration and withdrawal of the anticipation rejection under the doctrine of inherency.

Next, the Examiner asserts that the invention is obvious over Waldmann (1993) as evidenced by Waldmann (1995) and Vriesendorp. The Examiner takes the position that "one of

ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention" and that it would be "readily apparent to one of ordinary skill in the art at the time the invention was made". Applicant is concerned about the genuineness of such arguments. From the scientific view, the Examiner's statements are reckless. How could it be readily apparent to one of ordinary skill in the art that 5-15 mCi ^{90}Y conjugated to 20 mg of anti-Tac should be administered to a patient *if and only if* the patient has soluble IL-2R levels of over 50,000 U/ml from a reference that does not make any correlation to soluble IL-2R levels and does not teach the use of labeled anti-Tac in any particular amount? How could one expect to make this leap with "a reasonable expectation of success"? This invention is in the biomedical arts, which like the chemical and biotechnology arts is unpredictable in its very nature. Extensive patient studies are used to arrive at dosing schemes. The medical practice would not reach the claimed invention from reading the Waldmann (1993) reference.

From a legal view, the rejection is also improper. Obviousness cannot be predicated upon inherency. *In re Rijckaert*, 28 USPQ.2d 1955, 1957 (Fed. Cir. 1993). Obviousness requires some explicit or implicit teaching or suggestion in the prior art of the invention as a whole. There is no basis in Waldmann 1993, viewed alone or in combination with Vriesendorp that would lead the skilled artisan to a reasonable expectation of success. To preclude patentability under 35 U.S.C. §103, there must be some predictability of success in any attempt to combine elements of reference processes. The view that success would have been "inherent" cannot substitute for a showing of reasonable expectation of success. *In re Rinehart*, 531 F.2d 1048, 1054 (C.C.P.A. 1976). Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 27 has been rejected under 35 U.S.C.§102(f) because the applicants did not invent the claimed subject matter. Applicant respectfully disagrees with this rejection. However, in order to expedite prosecution of the claim, applicant submits herewith a Declaration from the named inventor, Dr. Thomas Waldmann, stating that he alone conceived of the claimed invention. The other persons named in the cited reference did not contribute to the conception of the claimed invention but rather acted under his direction in developing the algorithm discussed in the reference. Applicants respectfully request reconsideration and withdrawal of this §102(f) rejection.

Claim 27 has been rejected under 35 U.S.C.§103(a) as being unpatentable over Waldmann (Blood, 1993) and/or Waldmann (Imp. Adv. Oncol., 1994) and/or Waldmann (Leukemia, 1993) and/or Waldmann (Ann. Oncol., 1994) in view of Vriessendorp and Rubin. Applicants respectfully disagree with this rejection.

The Examiner asserts that "the combined references provide a sufficient expectation of success in achieving 2-20 mg anti-Tac encompassed by the claimed methods given the prior art teaching of administering 5-15 mCi doses of ^{90}Y anti-Tac antibody to ATL patients". Yet the Examiner admits that the four Waldmann references "differ from the claimed methods by not disclosing the particular mg amount of the 5-15 mCi doses of ^{90}Y anti Tac antibody." Nevertheless, the Examiner concludes "the clear prior art teachings of treating with ^{90}Y anti-Tac antibody would have been expected to fall within the 2-20 mg of anti-Tac antibody". This reasoning makes leaps that the skilled artisan simply would not take. How could the skilled artisan reach the specific claimed dosage determination, including the different dosages for different sIL-2 levels from the references cited? None of these references teach or

suggest the specific activity of the ^{90}Y conjugate as claimed. None of the references teach or suggest the correlation between sIL-2R levels and conjugate dose.

The Examiner points to Waldmann (1993) as an example of the teachings he relies on in concluding the claimed invention was obvious. The Examiner asserts that Waldmann (1993) describes the use of 20 mg of unlabeled anti-Tac, describes conjugating cytotoxic agents to anti-Tac, and describes a 2-17 mg anti-Tac requirement to achieve circulating bioavailable levels in a patient. From this, the Examiner concludes that "it would be readily apparent to one of ordinary skill in the art at the time the invention was made that the Waldmann et al (1993) that the claimed 2-20 mg is met by the prior art teaching of treating ATL patients with 5-15 mCi doses of ^{90}Y anti-Tac antibody". Applicant respectfully disagrees with this summary of the cited reference.

Waldmann (1993) describes the results of a study which used unlabeled anti-Tac in patients having a broad range of sIL-2R levels (i.e. from 920- 230,370 U/ml). The statement regarding the use of 2-17 mg of anti-Tac relates to a parallel study carried out to determine the minimum amount of anti-Tac necessary to detect bioavailable circulating anti-Tac. This level is quite different than the amount of anti-Tac necessary (and used in Waldmann (1993)) *to saturate sIL-2R* and thus treat the disease. Throughout the Waldmann (1993) reference, the researchers use unlabeled antibody and as the study progresses choose higher doses (i.e. 50 mg) for treatment. If the use of lower doses had been as obvious as the Examiner asserts, why did Waldmann select the higher doses? Reading the reference as a whole, the skilled artisan would conclude that the higher doses were necessary to achieve therapeutic results. Thus, in contrast to the Examiner's position, there is no motivation in the cited Waldmann references to select the lower doses for therapeutic treatment methods.

The Examiner also asserts that the cited Waldmann references "teach [that] elevated levels of the soluble IL-2R was associated with neoplastic disorders" and that Rubin reviews that "soluble IL-2 receptors were measured in a number of human diseases, including the malignancies encompassed by the claimed invention." From this, the Examiner concludes that "the soluble IL-2 receptor levels encompassed by the claimed methods were expected levels of malignant patients at the time the invention was made." While it is true that levels of IL-2R for patients with malignancies were known (*see* e.g. Table 1 of Waldmann (1993)), none of the cited prior art made any correlation between these sIL-2R levels and a particular dosage of ^{90}Y conjugated anti-Tac. Thus, the skilled artisan could not have recognized such a correlation from the cited art. Indeed, the Waldmann (1993) reference would have led the skilled artisan to conclude that there was NO correlation between sIL-2R levels and anti-Tac dosage, because despite the broad range of patient sIL-2R levels, the patients received a uniform dose of anti-Tac.

In sum, the cited prior art does not teach or suggest (1) a correlation between a patient's soluble IL-2 receptor levels and a particular dose of ^{90}Y-conjugated anti-Tac; or (2) the use of a ^{90}Y-conjugated Tac antibody provided at a specific activity of 5-15 mCi ^{90}Y and 2-20 mg of Tac antibody. Therefore, the cited prior art does not anticipate or make obvious the pending claim. Applicant respectfully requests reconsideration and withdrawal of the §103 rejection.

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this response, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2026-4003US3.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition and for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2026-4003US3. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: February 28, 2001

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